Mouse Models of Psoriasis

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Psoriasis is a T-cell-mediated chronic inflammatory skin disease believed to be of autoimmune nature that can be triggered or worsened by streptococcal throat infections. In addition to conventional chronic inflammatory changes, psoriasis is characterized by complex and striking alterations in epidermal growth and differentiation. Psoriasis is generally not observed in animals other than man, and this lack of a suitable animal model has greatly hindered research into the pathogenesis of psoriasis. Multiple transgenic, knockout, and reconstituted models of psoriasis have been developed over the past two decades. Despite their limitations, these models have demonstrated that keratinocyte hyperplasia, vascular hyperplasia, and cell-mediated immunity in the skin are closely interrelated. Xenograft models, in which involved and uninvolved psoriatic skin are transplanted onto immunodeficient mice, are the only models that come close to incorporating the complete genetic, immunologic, and phenotypic changes of the disease. They have shown conclusively that psoriasis is a T-cell-mediated disease, and have been used to elucidate novel pathogenic pathways. In this review, we describe various animal models, detail the immunologic and intracellular pathways that mediate these phenotypes and assess the utility of these models to better understand this disease.

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Abbreviations: AP, activator protein; BMP, bone morphogenetic protein; CsA, cyclosporine A; ERK, extracellular regulated kinase; HB-EGF, heparin-binding epidermal-like growth factor; IKK, IκB kinase; IRF, interferon regulatory factor; K, keratin; LFA, lymphocyte function-associated antigen; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; MIP, macrophage inflammatory protein; NGF, nerve growth factor; NN, non-psoriasis skin; NK, natural killer; NOD, non-obese diabetic; NP, non-lesional psoriasis skin; PP, plaque psoriasis skin; SCID, severe combined immunodeficiency; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

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INTRODUCTION

With two reported exceptions, a rhesus monkey (Lowe *et al.*, 1981) and a cynomolgus monkey (Zanolli *et al.*, 1989), psoriasis has not been observed in animals other than humans. This lack of a suitable animal model has greatly hindered research into the pathogenesis of psoriasis. However, over the past two decades, numerous mouse models have been identified or created by genetic engineering that mirror several aspects of psoriasis. Before these mouse models are discussed in detail, it is important to realize the profound differences that exist between mouse and human skin (Figure 1). Aside from the obvious size difference between mice and humans, the epithelium in fur-covered mouse skin is disproportionately composed of densely distributed hair follicles, whereas epithelium in human skin is to a much greater extent interfollicular. This difference is important as human epidermis shows differential expression of proteins in the outer root sheath of the follicles compared with the interfollicular areas (Schon *et al.*, 1995). Mouse skin does not share this feature, nor do the short inter-follicular regions contain any rete ridges. Mouse epidermis generally comprises of only 2–3 keratinocyte layers and is only one quarter the thickness of human epidermis, and has a faster epidermal turnover (Berking *et al.*, 2002). Furthermore, non-epithelial cutaneous tissue compartments also show profound cross-species differences. Human dermis is substantially thicker than mouse dermis and contains fewer hair follicles, and wounding is markedly different as mouse skin regenerates effectively without significant scarring (Khavari, 2006). Finally, mice have an entire cutaneous muscle layer, the panniculus carnosus that is only present in a rudimentary form in humans as the platysma and other small muscles of the face and neck.

Likewise, the immune system in mice differs from that of humans in several ways. For example, mice have several different subtypes of dendritic cells, including the $CD8^+$ dendritic cells and other inflammatory cells, such as the dendritic epidermal T cells and $NK1.1^+$ T cells that are not found in humans (Godfrey *et al.*, 2000; Ardavin, 2003; Jameson *et al.*, 2004). Another factor is that humans are outbred, whereas many of the mouse models discussed are on inbred or congenic backgrounds. Importantly, these models are usually based on manipulation of a single gene, whereas psoriasis, in contrast, is thought to result from interaction of multiple susceptibility loci (Bowcock and Cookson, 2004). Furthermore, rodents can be, and usually are, raised under controlled conditions, whereas humans are not.

For an animal model to be useful as a tool for the study of psoriasis, it should reflect many of the key histological

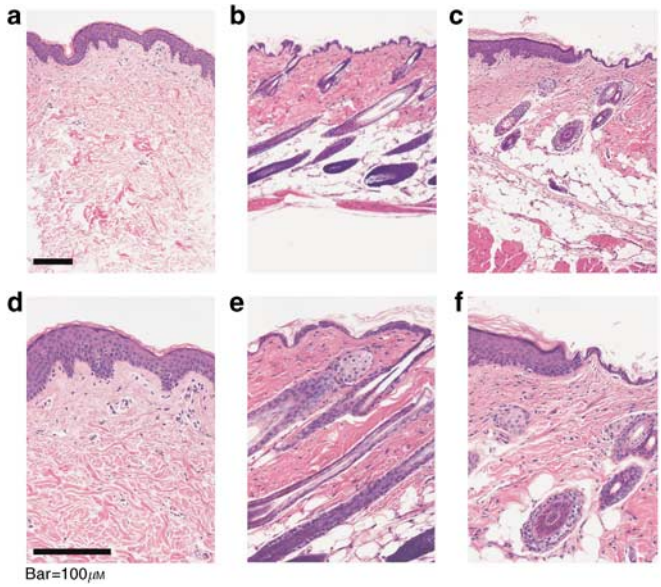

Figure 1. Histological comparison of normal human (a, d), mouse skin (b, e) and human-mouse xenograft (c, f). The figure shows a 0.4-mm-thick human skin xenograft 42 days after transplantation into a NOD/LtSz-*Prkdc*^{scid}/*Prkdc*^{scid} recipient, and serves to illustrate some of the differences in the anatomy of human *versus* mouse skin described in the text. Note that no human follicles are visible in the xenograft shown, which was derived from a keratome biopsy of buttocks skin. Mouse epidermis generally comprises only three cell layers and is $<25\,\mu$m in thickness, whereas human epidermis commonly constitutes 6–10 cell layers and is $>50\,\mu$m thick. It is also noteworthy that the short inter-follicular regions in mouse skin do not contain any rete ridges. Human dermis is substantially thicker than mouse dermis and contains fewer hair follicles. Finally, mice contain an entire cutaneous muscle layer, the panniculus carnosus.

features of the disease. Histologically, psoriasis is characterized by uniform elongation of rete ridges with thinning of the suprapapillary epidermis. The tips of the rete ridges are often clubbed or fused with adjacent ridges with edematous dermal papillae containing dilated, tortuous capillaries, but despite the edema, spongiosis (build up of fluid between keratinocytes) is mild or absent. Parakeratosis (retention of nuclei in the stratum corneum) is another characteristic together with thinning or absence of the granular layer. Parakeratosis may be confluent or may alternate with orthokeratosis (nuclei absent), and is inversely correlated with presence of the granular layer (Cox and Watson, 1972). Collections of neutrophils in the parakeratotic stratum corneum (Munro's microabscesses) are very common, and may occur, albeit less frequently, in the spinous layer, where they may form spongiform pustules of Kogoj (Gillum and Golitz, 2004). The altered pattern of epidermal differentiation seen in psoriasis has been termed regenerative maturation, because it bears striking similarities to wound healing (Mansbridge *et al.*, 1984). Several molecular components of this response (i.e., induction of the ''hyperproliferative'' keratins 6, 16, and 17, and altered expression of the epidermal differentiation markers loricrin, involucrin, and filaggrin) are excellent markers for therapeutic response in psoriasis (Vallat *et al.*, 1994). Furthermore, any useful model of this disease should also reproduce the immunologic features of psoriasis, and therefore respond to the same treatments that have been shown to be effective in psoriasis.

In this review, we describe the various mouse models that have been developed and reported to show features reminiscent of psoriasis, we detail the immunologic and intracellular pathways that mediate these phenotypes, and assess the utility of these models to further our understanding of this enigmatic disease.

Spontaneous mouse models

A number of spontaneous mouse mutations that give rise to psoriasiform phenotypes have been described (Sundberg and King, 1996; Raychaudhuri *et al.*, 2001). These were the first mice to hold the promise that an animal model of psoriasis was obtainable.

The flaky skin (*Ttc7*^{fsn}/*Ttc7*^{fsn}) mouse displays a progressive papulosquamous skin disorder. The hair shafts of these mice have pits, striations, and outward growing protrusions. Nails are bent at a 90° angle and have surface irregularities with accumulation of scale at the nail base. The skin exhibits intraepidermal invasion by neutrophils, increased epidermal growth factor (EGF) receptor levels, and interestingly, a positive Koebner reaction after tape-stripping, which resolves after 6 weeks of treatment with oral, but not topical, cyclosporine A (CsA), topical EGF, or UVB exposure (Sundberg *et al.*, 1994). Flaky skin mouse keratinocytes have mitochondrial aberrations, and homozygotes also suffer anemia and forestomach hyperplasia.

The spontaneous chronic proliferative dermatitis mutation (*cpdm*/*cpdm*) is characterized by redness, alopecia, scaling, and severe pruritus (HogenEsch *et al.*, 1993). Histologically, epithelial hyperproliferation is accompanied by infiltration of eosinophils, macrophages, and mast cells, but only very few T cells. Lesions similar to those in the skin occur in the esophagus and forestomach (HogenEsch *et al.*, 1993). The phenotype could be reversed to some extent with corticosteroid treatment, but CsA was wholly ineffective. Topical calcipotriene decreased cell proliferation, but had no effect on epidermal thickness (Gijbels *et al.*, 2000).

Homozygous asebia (*Scd1*^{ab}/*Scd1*^{ab}) mutant mice (Gates and Karasek, 1965) are small, hunched, and have hypoplastic sebaceous glands resulting from a defect in the stearoyl coenzyme A desaturase-1 (*Scd1*) gene (Zheng *et al.*, 1999). Adult homozygotes develop scaly skin with generalized alopecia. Histologically, the epidermis is thickened with enlarged intercellular spaces and excessively long hair follicles extending at a sharp angle into the deep subcutis. The mutant mice have a thickened dermis characterized by increased vascularity, increased cellularity, and prominent fibroblasts. The dermal cellular infiltrate is rich in mast cells and macrophages, but lacks T cells and neutrophils (Brown and Hardy, 1988, 1989).

These spontaneous mutants often displayed some histological features of psoriasis such as acanthosis, infiltration of mast cells and macrophages, and increased vasculature (Sundberg *et al.*, 1990). However, the general absence of T cells in the infiltrates (Wilkinson and Karasek, 1966;

Sundberg *et al.*, 1994) and lack of efficacy of anti-psoriasis drugs (CsA, calcipotriene, and etretinate) (Gijbels *et al.*, 2000) suggest that these mice do not recapitulate all the pathologic features of psoriasis.

Genetically engineered mouse models of psoriasis

Over the past two decades, various transgenic and gene knockout mouse models have been created that demonstrate some of the pathologic features observed in psoriasis. In most of these models, either increased expression or knockout of specific genes is directed to the basal layer of the epidermis using promoters for the keratin genes *KRT5* or *KRT14*, or to the suprabasal layer using *KRT1*, *KRT10*, or involucrin (*IVL*) promoter sequences. The similarity of these models to actual psoriasis is compared in Figure 2. Further details of the transgenes and targeted mutations for the models described here can be found in Tables S1 and S2, respectively.

Targeted manipulation of the Stat3 pathway

Signal transducers and activators of transcription (STATs) constitute a family of latent cytoplasmic proteins involved in transmitting extracellular signals to the nucleus (Levy and Darnell, 2002). One member, Stat3 (Figure 3a), has a critical role in various biological activities, including cell proliferation, survival, and cell migration (Leonard and O'Shea, 1998; Hirano *et al.*, 2000; Turkson and Jove, 2000; Levy and Darnell, 2002). Persistent activation of Stat3 has been implicated in carcinogenesis of squamous cell carcinoma of the head and neck (Song and Grandis, 2000). In the skin, Stat3 has an essential role in wound healing (Sano *et al.*, 1999, 2001) and is activated in psoriasis (Sano *et al.*, 2005a). It has also been shown to be a key regulator of keratinocyte proliferation and survival following ultraviolet light B irradiation (Sano *et al.*, 2005b). Recently, a transgenic mouse was developed, in which a constitutively active Stat3 mutation was expressed in basal keratinocytes using a bovine *KRT5* promoter: *Tg(KRT5-Stat3*A661C*N663C)1Jdg* (Table S1) (Sano *et al.*, 2005a). These mice developed skin lesions resembling psoriasis either spontaneously or in response to wounding by tape-stripping. The skin lesions showed keratinocyte hyperplasia (acanthosis) with loss of the granular layer and parakeratosis. Dilated blood vessels were prominent, and a leukocytic infiltrate of lymphocytes and neutrophils was observed. Most of the lymphocyte infiltrate consisted of $CD4^+$ T cells in the upper dermis and epidermis, whereas the few $CD8^+$ T cells that were seen were localized predominantly within the epidermis. No phenotype was seen when skin of these mice was transplanted onto immunodeficient mice, but when activated T cells from the Stat3 mutant mice were injected intradermally underneath the graft, the psoriatic phenotype of the graft was generated. Thus, the development of skin lesions in this model is dependent on T-cell activation.

In another transgenic mouse model in which expression of IL-20 was targeted to the basal layer using a *KRT14* promoter, *Tg(KRT14-Il20)1Yac*, aberrant keratinocyte differentiation was seen (Blumberg *et al.*, 2001). IL-20 and its receptors are overexpressed in psoriatic skin (Blumberg *et al.*, 2001), and IL-20 is a potent activator of Stat3 (Blumberg *et al.*, 2001) (Figure 3a). In this model, abnormal keratinocyte differentiation with expression of the regenerative maturation marker K6 was seen. These mice also had thickened hyperkeratotic epidermis and compact stratum corneum (Blumberg *et al.*, 2001). The stimulatory effect of IL-20 on the proliferation of cultured keratinocytes was enhanced by IL-1β, EGF, and tumor necrosis factor (TNF)-α (Blumberg *et al.*, 2001). In a similar model, in which IL-6 was expressed in the basal layer under the control of a *KRT14* promoter, *Tg(Il6)1Efu*, minimal skin findings were seen apart from thickened stratum corneum (Turksen *et al.*, 1992). IL-6 is also a known activator of Stat3 (Heinrich *et al.*, 1998) and can also activate the extracellular regulated kinase-mitogen activated protein kinase pathway (Hirano *et al.*, 2000). IL-6 has been reported to be highly expressed in psoriatic epidermis (Grossman *et al.*, 1989), although other studies have not been able to confirm this (Gearing *et al.*, 1990; Elder *et al.*, 1992). These contradictory findings may be explained by a report that IL-6 expression is greatest at the margins of psoriatic plaques (Ohta *et al.*, 1991). Interestingly, IL-6 has also been shown to stimulate proliferation of cultured keratinocytes (Grossman *et al.*, 1989; Elder *et al.*, 1992) and, therefore, has a plausible role in the pathogenesis. However, unlike the Stat3 mutant mouse discussed above, no inflammatory infiltrates were observed in either the *Tg(Il6)1Efu* (Turksen *et al.*, 1992) or the *Tg(KRT14-Il20)1Yac* (Blumberg *et al.*, 2001) transgenic mice.

Leptin is another potent inducer of Stat3 in keratinocytes (Goren *et al.*, 2003; Figure 3a). Leptin is a major adipocyte-derived cytokine that is involved in the regulation of food intake and energy expenditure. Leptin-deficient B6.V-*Lep*^{ob}/J mice have severely delayed wound healing that can be reversed by systemic or topical delivery of leptin (Frank *et al.*, 2000). In skin, the leptin receptor is exclusively expressed in keratinocytes of the basal layer of the epidermis and the hyperproliferative epithelium at the wound edge (Frank *et al.*, 2000). In a transgenic model that targeted overexpression of leptin to basal keratinocytes, *Tg(KRT5-Lep)1Flar*, no observable effects on skin differentiation or proliferation were seen (Rico *et al.*, 2005), but wound healing impairment was observed, probably secondary to leptin resistance. The role of the leptin–leptin receptor system in psoriasis has not yet been determined.

The features seen in these transgenic animals indicate that signaling through the Stat3 pathway can result in some of the features typically seen in psoriasis, including hyperproliferation of keratinocytes and altered differentiation. It is noteworthy that in the Stat3 mutant mouse above, the phenotype was dependent on immunocyte infiltration, but no such infiltrate was seen in the *Tg(Il6)1Efu*, *Tg(KRT14-Il20)1Yac*, or *Tg(KRT5-Lep)1Flar* transgenic models. This is somewhat surprising, given that these three cytokines are known to activate Stat3 *in vitro*. Given that the latter models are dependent on ligand–receptor interaction, excess ligand can lead to resistance to its effect and therefore a minimal or even reverse phenotype as was observed in the leptin model. It is also possible that, in addition to Stat3, the ligand–receptor

	Model	Epidermal changes: Thickening	Epidermal changes: Altered differentiation	Epidermal changes: Rete ridges	Epidermal changes: Papillomatosis	Vascular changes: Dilation of capillary loops	Inflammatory changes: Epidermal T-cell infiltrate	Inflammatory changes: Intraepidermal microabscesses	"Koebner" phenomenon	Phenotype dependent on immune activation	Features unlike human psoriasis
	Human psoriasis	Y	Y	Y	N	Y	Y	Y	Y	Y	
Xg	PN on CB.17-*Prkdc*^{scid} (Wrone-Smith and Nickoloff, 1996)	Y	Y	Y	N	Y	Y	Y	?	Y	
Xg	PN on AGR129 (Boyman *et al.*, 2004)	Y	Y	Y	N	Y	Y	Y	Y	Y	
Alg	CD4^{+}CD45RB^{hi} on ICR-*Prkdc*^{scid} (Schon *et al.*, 1997)	Y	Y	Y	N	Y	Y	Y	?	Y	Colon inflammation, splenomegaly, no CD8^{+} T cells
Transgenic	K5-Stat3C (Sano *et al.*, 2005a)	Y	Y	Y	N	Y	Y	Y	Y	Y	Alopecia
Transgenic	K14-IL-20 (Blumberg *et al.*, 2001)	Y	Y	N	N	N	N	N	N	N	Neonatal lethality
Transgenic	K14-IL-6 (Turksen *et al.*, 1992)	Y	N	N	N	N	N	N	N	N	No hyperproliferation
Transgenic	K5-latent TGF-β1 (Li *et al.*, 2004)	Y	Y	Y	?	Y	Y	Y	Y	?	Alopecia
Transgenic	K10-BMP-6 (Blessing *et al.*, 1996)	Y	Y	N	N	Y	Y	Y	?	?	Alopecia
Transgenic	Involucrin-integrins (Carroll *et al.*, 1995)	Y	Y	N	N	Y	Y	Y	?	?	Retarded growth, hair abnormalities, corneal damage
Transgenic	Involucrin-MEK1 (Hobbs *et al.*, 2004)	Y	Y	N	Y	?	Y	?	?	?	No parakeratosis, increased loricrin and filaggrin
Transgenic	Involucrin-amphiregulin (Cook *et al.*, 2004)	Y	Y	N	Y	Y	Y	Y	?	?	Early lethality, alopecia, synovitis
Transgenic	K14-IL-1α (Groves *et al.*, 1995)	Y	Y	N	N	N	?	N	N	?	Crusts, scarring, alopecia, weight loss
Transgenic	Haptoglobin-collagenase (D'Armiento *et al.*, 1995)	Y	Y	N	?	N	N	N	?	N	Early lethality
Transgenic	K14-amphiregulin (Cook *et al.*, 1997)	Y	Y	N	Y	Y	Y	Y	?	?	Early lethality, alopecia, mild synovitis
Transgenic	K14-VEGF (Xia *et al.*, 2003)	Y	Y	Y	N	Y	Y	Y	Y	?	Wounding needed in younger mice
Transgenic	Tie2 (Tek) (Voskas *et al.*, 2005)	Y	Y	Y	N	Y	Y	Y	Y	?Y	Hair loss, age-related cataracts
Transgenic	Involucrin-IFN-γ (Carroll *et al.*, 1997)	Y	Y	N	N	Y	N	?	?	?	Retarded growth, alopecia
Transgenic	K14-p40 (Kopp *et al.*, 2001)	Y	?	?	?	?	Y	?	?	?	Crusts, alopecia, no CD8^{+} T-cell infiltrate
Transgenic	HLA-B*27 and β_2m (Breban *et al.*, 1996)	Y	Y	Y	N	Y	Y	Y	?	?	Multiorgan inflammatory disease
Transgenic	TCR MM14.4 (Logunova *et al.*, 2005)	Y	Y	N	N	?	Y	Y	?	Y	Alopecia
Targeted mutations	Hypomorphic CD18 (Bullard *et al.*, 1996)	Y	Y	N	?	Y	Y	Y	?	Y	Alopecia and crust formation.
Targeted mutations	Targeted Junb, Jun KO (Zenz *et al.*, 2005)	Y	Y	?	N	Y	Y	Y	?	N	Alopecia, spongiosis, IL-12p35 and IL-18 absent, TNF-α and T-cell independent
Targeted mutations	IL-1ra KO (Shepherd *et al.*, 2004)	Y	Y	Y	N	Y	Y	Y	?	?	Infiltrate of mixed Th1 and Th2 cells, few CD8+ T cells
Targeted mutations	Integrin α_E KO (Schon *et al.*, 2000)	Y	Y	?	?	?	Y	Y	?	?	Mixed Th1 and Th2 cytokines, few epidermal CD8+ T cells
Targeted mutations	IRF-2 KO (Hida *et al.*, 2000)	Y	Y	?	?	?	Y	?	?	Y	Alopecia, ulceration, disorganized muscle layer with fibrosis
Targeted mutations	Targeted IKK2 KO (Pasparakis *et al.*, 2002)	Y	Y	N	N	?	N	Y	?	Y	Apoptosis in epidermis, early death. T-cell independent
Spontaneous	Flaky skin(*Ttc7*^{fln}/*Ttc7*^{fln}) (Sundberg *et al.*, 1997)	Y	Y	N	Y	Y	N	Y	Y	N	Anemia, alopecia, multiorgan
Spontaneous	Chronic proliferative dermatitis (*cpdm/cpdm*) (HogenEsch,1993)	Y	Y	?	?	Y	N	Y	Y	N	Severe pruritus, few infiltrating T cells
Spontaneous	Homozygous asebia (*Scd1*^{ab}/*Scd1*^{ab}) (Brown and Hardy, 1988, 1989).	Y	N	N	N	Y	N	N	?	?	Alopecia, hypoplastic sebaceous glands, long hair follicles, photophobia. Smaller size

Figure 2. Summary of various mouse models and their resemblance to human psoriasis – modified and expanded from Xia *et al.* (2003). The first row indicates the characteristic changes seen in human psoriasis (Y, yes; N; no). Other models are compared with the human standard and are blocked in green if they match human psoriasis or in red if they do not match. Question marks and the yellow blocks indicate that the feature in question was not examined. It is noteworthy that several models have most of the listed features of psoriasis, although several of the features seen in the mice, like elongation of rete ridges, are not as marked as in the human disease and are often difficult to evaluate given the increased density of hair follicles in mice. Given these similarities, it is remarkable that only the xenograft models have so far been successfully used to investigate novel therapeutic agents. Further details of the models based on **appear in Table S1 (transgenics) and 2b (targeted mutations). Xg: xenograft, Alg: MHC-mismatched allograft, and Sp: spontaneous mouse models.

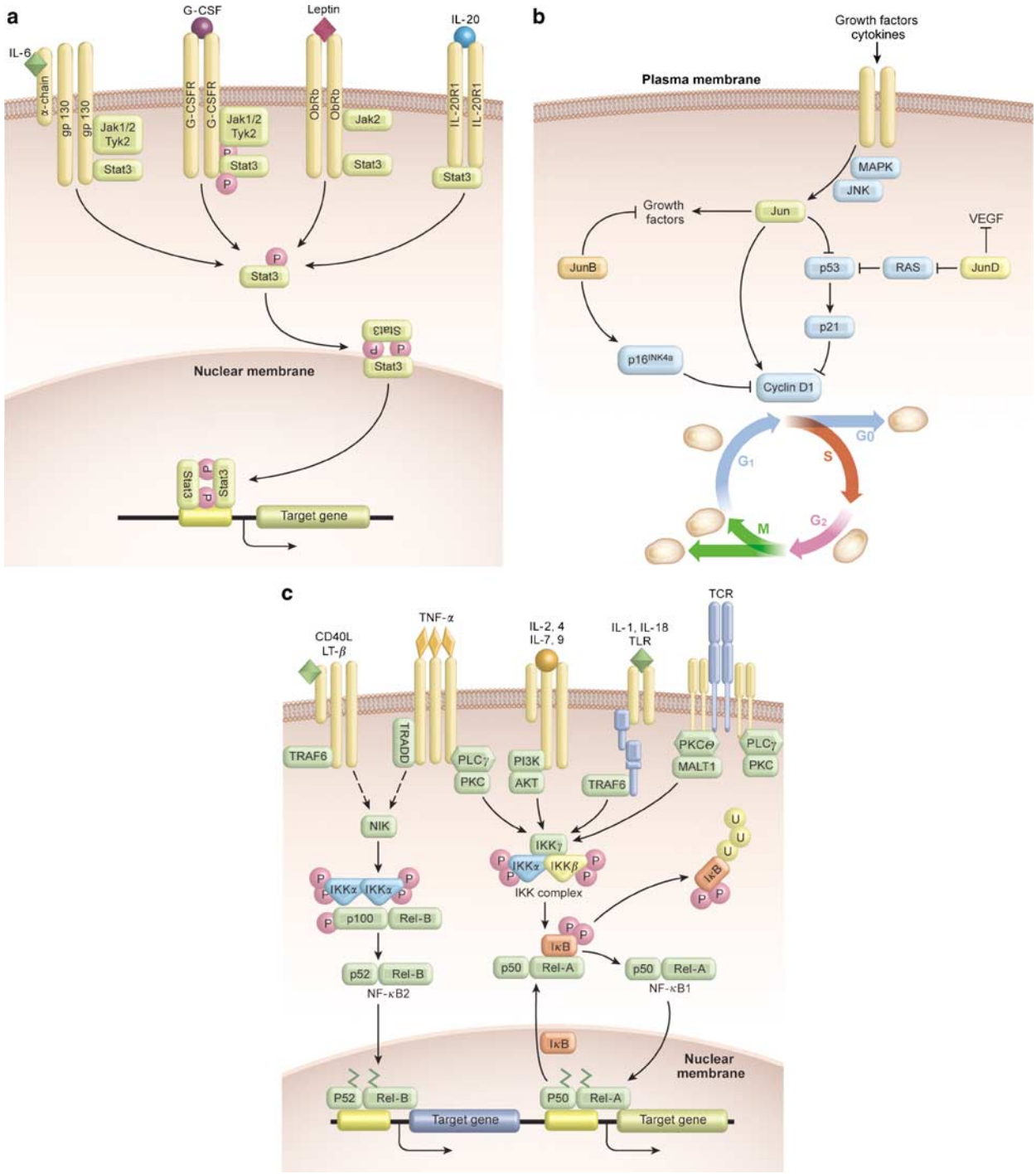

Figure 3. Some of the biochemical pathways manipulated in transgenic mouse models of psoriasis: STAT3, AP-1 and the NF-κB pathways. (**a**) Extracellular components that activate STAT pathways include granulocyte colony stimulating factor (G-CSF) (Kamezaki *et al.*, 2005), leptin (Goren *et al.*, 2003), IL-6 (Sriuranpong *et al.*, 2003), and IL-20 (Blumberg *et al.*, 2001). Stat3 is activated through phosphorylation, followed by dimerization and nuclear translocation (Levy and Darnell, 2002). (**b**) The Jun proteins (Jun, JunB, and JunD), together with the Fos proteins (Fos, FosB, Fra1, and Fra2) and some members of the ATF and CREB protein families are the principal components of the AP-1 transcription factor family (Jochum *et al.*, 2001). Jun plays an essential role in cell proliferation by influencing a number of cell cycle regulators such as p53 and cyclin D1, whereas JunB negatively regulates cell growth by activating the $p16^{INK4a}$ inhibitor and decreasing cyclin D1 expression (Weitzman, 2001). The balance of Jun proteins, with their opposing effects, has been proposed to determine whether cells progress through the cell cycle or die (Weitzman, 2001). Both Jun and JunB knockout mice have an embryonic lethal phenotype (Szabowski *et al.*, 2000). (**c**) A multitude of extracellular signals are transduced to the nucleus via NF-κB and, crucially, these are controlled by the IκB kinase (IKK) complex. IKK is activated by phosphorylation of its IKKα and IKK*β* subunits. IKK is then able to phosphorylate IκB, leading to its dissociation, ubiquitination, and destruction by the proteasome. Once liberated, the active NF-κB dimer (p50 and Rel-A(p65)) enters the nucleus and induces gene transcription. IKKα may also form homodimers, which are activated by NF-κB-inducing kinase (NIK) and lead to gene transcription by NF-κB2 (p52-Rel-B).

interactions simultaneously activate other intracellular pathways that serve to blunt leukocytic infiltration.

The AP-1 transcription factor family

Activator protein-1 (AP-1; Figure 3b) is a family of transcription factors known to play an important role in keratinocyte differentiation (Mehic *et al.*, 2005), and their DNA-binding activity has been reported to be decreased in psoriatic skin (Johansen *et al.*, 2004). In a recent paper (Zenz *et al.*, 2005), two members of the AP-1 family, JunB and Jun (c-Jun), were knocked out in the epidermis of postnatal mice (*Tg(Krt1-5-cre/ERT)1Ipc* with *Junb*^{tm3Wag} or *Jun*^{tm4Wag}, or both, Table S2). Single knockout mice had no observable changes, but Junb Jun double knockouts developed psoriasis-like features associated with severe arthritis. Lesional skin showed infiltration of neutrophils and lymphocytes with upregulation of several cytokines and chemokines typical for psoriasis. However, IL-12 and IL-18 were absent, and IFN-γ was only slightly upregulated and in a delayed manner. The same knockouts were established on immunodeficient mouse backgrounds, including TNF receptor 1 knockout and recombinase activating gene-*2* (*Rag2*) knockout, which do not have any functional T cells. This resulted in decreased joint inflammation but minimal changes in the skin inflammation, thus demonstrating that the inflammation in this model was independent of T-cell function. The authors, therefore, suggested that T cells might not be essential for triggering psoriasis in humans. Given the considerable evidence for a key role of T cells in the pathogenesis of psoriasis (Gudjonsson *et al.*, 2004), the relevance of this model to psoriasis has been questioned (Gudjonsson and Elder, 2005; Haider *et al.*, 2006). Furthermore, other studies have reported unchanged or even increased levels of Jun and JunB in psoriasis (Basset-Seguin *et al.*, 1991; Johansen *et al.*, 2004; Kulski *et al.*, 2005; Haider *et al.*, 2006). The marked phenotype seen in this animal model, which in many ways resembles the regenerative maturation phenotype seen in psoriasis, raises the possibility that one of the many genetic components that predispose to psoriasis may involve a component of the AP-1 transcription family. The role of AP-1 may extend beyond the keratinocyte itself to involve intercellular communication between the epidermis, mesenchyme, and the inflammatory infiltrate (Schuh *et al.*, 1990; Greenhalgh *et al.*, 1993; Szabowski *et al.*, 2000).

Manipulation of the NF-κB pathway

IκB kinase (IKK) is a negative regulator of the NF-κB signal transduction pathway and consists of the two catalytic subunits (IKKα and IKKβ) and a regulatory subunit (IKKγ/NEMO (NF-kappaB essential modulator)) (Figure 3c). The IKKα and IKKβ units phosphorylate IκB, targeting it for degradation and thus inducing activation of NF-κB (reviewed in Hayden and Ghosh, 2004). Mice with an epidermis-specific deletion of IKKβ (*Tg(KRT14-cre)1Cgn* with *Ikbkb*^{tm1Mpa}; Table S2) develop a severe inflammatory skin disease, which is dependent on the dermal expression of TNF-α (Pasparakis *et al.*, 2002) and accumulation and activation of dermal macrophages (Stratis *et al.*, 2006). Although the epidermis of these mice showed altered differentiation and thickening, it had several characteristics, including keratinocyte apoptosis, T-cell-independent inflammation, and early death, which made it incompatible with psoriasis (Figure 2). On the other hand, IKKα-deficient mice (*Chuk*^{tm1Ver}; Table S2) showed abnormalities in epidermal morphogenesis without inflammation, thus also not resembling psoriasis (Li *et al.*, 1999). There are indications that the DNA-binding activity of NF-κB is regulated in a specific manner in psoriasis skin depending on the specific DNA-binding sites investigated, not accompanied by any change in the expression of the IKK proteins (Johansen *et al.*, 2005).

TGF-β and related mouse models

Transforming growth factor (TGF)-β1, β2, and β3 are members of a large family of highly conserved yet pleiotropic cytokines (Figure 4a). One or more of the TGF-β family receptors and ligands are expressed in almost every tissue in the body, and TGF-β1 has pivotal roles in T-cell development and homeostasis (Gorelik and Flavell, 2002), and growth of epithelial and endothelial cells (Miyazono *et al.*, 2001). Expression of TGF-β1 or its receptors or both has been found to be increased (Kane *et al.*, 1989), unaffected (Elder *et al.*, 1989), or decreased in psoriatic skin (Doi *et al.*, 2003). Several transgenic mouse models have been engineered that target a constitutively active form of TGF-β1 (containing C223S and C225S mutations) to the epidermis (Table S1). When constitutive expression of active TGF-β1 was targeted to suprabasal keratinocytes using the *Tg(Tgfb1)1Der* transgene, the mice died within 24 h of birth due to inhibition of normal skin development (Sellheyer *et al.*, 1993). Similarly, in an inducible TGF-β1 system, *Tg(tk-TGF-B1)c1849Der* $\times$ *Tg(Lor-Gal4/PGR/VP16)c4486Der*, sustained suprabasal expression of the TGF-β1 transgene exerted a growth-inhibitory effect on the epidermis (Wang *et al.*, 1999). However, other transgenic animals, for example, *Tg(KRT10-TGF-B1*C223S*C225S)1Rosa* (Cui *et al.*, 1995) and *Tg(KRT6-Tgfb1)4Rosa* (Fowlis *et al.*, 1996), have shown increased epidermal proliferation without hyperplasia when expression was directed to the suprabasal layer. In another conditional TGF-β1 system, using *Tg(tetO-TGF-B1*C223S*C225S)1Glk* $\times$ *Tg(KRT5-rtTA)1Glk* or *Tg(KRT5-tTA)1Glk* bitransgenic mice, active TGF-β1 expression was directed to the basal layer under the control of the (reverse) tetracycline transactivator. In this case, induction of TGF-β1 during gestation caused embryonic death, whereas induction in adult mice lead to keratinocyte proliferation, dermal fibrosis, inflammation, and loss of hair growth (Liu *et al.*, 2001). This was associated with upregulation of Smad7 (Liu *et al.*, 2001), an inhibitor of TGF-β1 signaling (Miyazono *et al.*, 2001), suggesting that the hyperproliferative phenotype might have resulted in part from the development of a sustained negative feedback loop. Expression of the latent form of TGF-β1 in the basal epidermal layer using *Tg(KRT5-TGF-B1)F2020Xjw* transgenic mice resulted in a striking psoriasis-like phenotype (Li *et al.*, 2004). These animals exhibited a thickened stratum

corneum with parakeratosis and a hyperplastic epidermis. Scattered mononuclear cells were seen in the epidermis and subcorneal microabscesses containing mixed mononuclear cells and neutrophils, and prominent neovascularization. Langerhans cells were sparse in the transgenic epidermis, a feature also observed in human psoriasis (Gordon *et al.*, 2005). Integrin $\alpha_E\beta_7$ expression was seen on epidermal T cells in addition to upregulation of cytokines and chemokines, characteristic of psoriasis; IL-1α, including macrophage inflammatory protein-1β (MIP-1β, CCL4), TNF-α, IFN-γ, and vascular endothelial growth factor (VEGF). Interestingly Smad7 expression was moderately upregulated, as was the keratinocyte growth factor amphiregulin (Li *et al.*, 2004).

Bone morphogenetic protein-6, another member of the TGF-β superfamily, has also been overexpressed in the suprabasal epidermis under the control of the *KRT10* promoter (*Tg(KRT10BMP6)VI632Mbl*) (Blessing *et al.*, 1996; Wach *et al.*, 2001). Depending on the pattern of transgene expression, the effects on proliferation and differentiation were opposite. Strong and uniform expression of the bone morphogenetic protein-6 transgene resulted in severe repression of cell proliferation with marginal effects on differentiation, whereas weaker and patchy expression of the transgene evoked strong hyperproliferation and parakeratosis. Severe perturbation of the usual pattern of differentiation was seen along with an inflammatory infiltrate in both dermis and epidermis. Interestingly, these mice were resistant to induced chemically skin carcinogenesis, most likely owing to a downregulation of AP-1 constituents (Wach *et al.*, 2001). Such resistance to neoplastic transformation is a feature of psoriasis, but the underlying mechanism is incompletely understood (Nickoloff, 2004).

These studies demonstrate that perturbations in TGF-β signaling can lead to abnormal differentiation and hyperproliferation of keratinocytes. On the basis of these models, it is apparent that constitutive overexpression of active TGF-β and related factors lead to a different phenotype than those engendered by low, intermittent, and or focal expression. Similarly, the metabolic form of TGF-β is also important. Interestingly, the psoriatic-like phenotype is more likely to be associated with the expression of Smad7, an inhibitory element of the TGF-β signaling pathway, rather than activation of Smad2 and Smad3 (Figure 4a). This is consistent

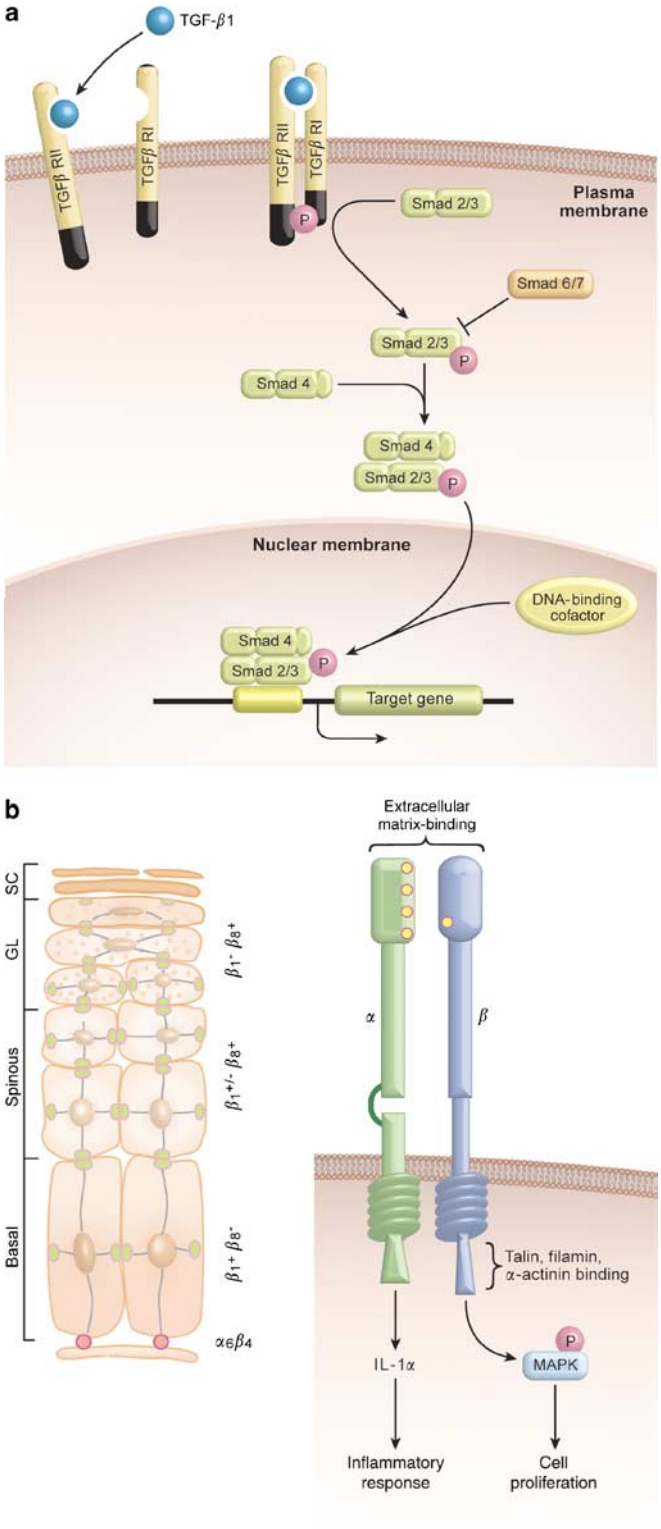

Figure 4. Some of the biochemical pathways manipulated in transgenic mouse models of psoriasis: TGF-β signaling and integrin pathways. (**a**) TGF-β1 is secreted in a latent form, which after release of a latency-associated peptide, signals via a heterodimeric receptor complex consisting of one of seven type I receptors (TGF-βRI, or activin receptor-like kinases, ALK) and a type II receptor (TGF-βRII). On binding a ligand, the type II receptor recruits and phosphorylates the type I receptors, which activate the downstream signaling mediators Smads 2, 3, and 4 (Kretzschmar and Massague, 1998). Interestingly, the known target genes for TGF-β1 are members of the AP-1 family (Wach *et al.*, 2001) (Jonk *et al.*, 1998; Ueyama *et al.*, 1998; Choi *et al.*, 1999; Hollnagel *et al.*, 1999). (**b**) Each integrin is a heterodimer of an α and a β subunit, which determine the ligand-binding specificity (Hynes, 1992, 2002). β_1 integrins are expressed throughout the proliferative compartment of the epidermis (Bata-Csorgo *et al.*, 1993). In healthy intact epidermis, β_1 is restricted to the basal layer; however, suprabasal integrin expression (spinous and granular layer, GL) is a feature of hyperproliferative epidermis as found in wound closure (Grose *et al.*, 2002), psoriasis (Pellegrini *et al.*, 1992), and neoplastic keratinocyte disorders (Bagutti *et al.*, 1998).

with human psoriatic lesions, in which TGF-β2 and TGF-β3 and their receptors are downregulated and Smad2 mRNA levels are decreased (Doi *et al.*, 2003). Another possibility is that the hyperproliferation is secondary to an effect on the dermis. Fibroblasts in transgenic skin, in addition to inflammatory cells, have been shown to contribute to epidermal hyperproliferation through production of growth factors, such as keratinocyte growth factor and insulin-like growth factor-1 (Miura *et al.*, 2000). These results highlight the complexity of TGF-β signaling in skin.

Transgenic expression of integrins, collagenase, and IL-1α

The integrins form a large family of cell-surface receptors that mediate cell–cell and cell–extracellular matrix adhesion. A number of integrin knockout mice with a range of epidermal phenotypes have been engineered (Hynes, 1992, 2002; Watt, 2002). Of particular interest are animals with altered expression of the β_1 integrins as these are typically restricted to the basal layer, and are involved in the control of keratinocyte proliferation and inhibition of terminal keratinocyte differentiation (Figure 4b; Levy *et al.*, 2000). In a transgenic mouse model where β1 expression was directed to the suprabasal layer of the epidermis (Table S1; Carroll *et al.*, 1995), the animals began to show flaking of the epidermis with inflammation after 6 weeks of age. Interestingly, some of the animals went through cycles of exacerbations and spontaneous remissions. Pathologically, the lesional skin showed several features of psoriasis, including parakeratosis and an inflammatory infiltrate characterized by neutrophilic pustules, $CD8^+$ T cells in the epidermis and $CD4^+$ T cells in the dermis (Carroll *et al.*, 1995). Increased activation of mitogen-activated protein kinase in basal and suprabasal keratinocytes was also seen (Haase *et al.*, 2001). MEK1 (MAP2K1) is an upstream kinase of the extracellular regulated kinase-mitogen-activated protein kinase. When a constitutively active, MEK1 mutant was expressed in the suprabasal epidermis (*Tg(IVL-MEK1*S217E*S221E)3062Fmw*), a phenotype very similar to the β1 integrin transgenics was seen (Hobbs *et al.*, 2004). In both models, increased production of IL-1α was seen. Interestingly, when the MEK1 model was crossed with another strain overexpressing the IL-1 receptor, exacerbated hyperproliferation and inflammation was seen (Hobbs *et al.*, 2004). Similarly, overexpression of IL-1α in the basal layer of the epidermis (*Tg(Il1a)1.1Tsk*; Table S1) led to hyperproliferation of keratinocytes, with infiltration of the macrophage/monocyte lineage (Groves *et al.*, 1995). Given the phenotype of the IL-1α transgenic mouse, it was not surprising that mice lacking the IL-1 receptor antagonist ($Il1rn^{tm1Nick}$) had psoriasis-like features, including hyperproliferative epidermis with inflammatory infiltrate (Shepherd *et al.*, 2004). This phenotype was dependent on the background mouse strain, with BALB/c being the only strain showing both cutaneous and joint inflammation (Shepherd *et al.*, 2004). In contrast to this, IL-1 activity has been shown to be reduced in psoriatic skin lesions, attributed to reduced IL-1α levels and the presence of IL-1 inhibitors (Cooper *et al.*, 1990). The IL-1/IL-1 receptor system contains many checks and balances, and further study is needed to understand how transgenic dysregulation of this system leads to psoriasis-like features.

When human tissue collagenase was overexpressed in mouse epidermis, psoriasis-like features were unexpectedly seen (D'Armiento *et al.*, 1995). Tissue collagenase is a matrix metalloproteinase (MMP1) expressed in most tissues that undergo remodeling and is expressed physiologically by keratinocytes involved in wound healing (Donoff *et al.*, 1971). When this enzyme was targeted to the suprabasal layer (*Tg(HP-MMP1)50Cha*; D'Armiento *et al.*, 1995), the mice (Haptoglobin-collagenase) had dry and scaly skin, with histology showing keratinocyte hyperproliferation and, interestingly, these animals had augmented sensitivity to epidermal carcinogenesis. Collagenase expression also caused disruption of the epidermal architecture in the transgenic mice, although there are no known fibrillar collagens within the epidermis. The underlying mechanism of the phenotype mediated by the expression of this enzyme would, therefore, be expected to be either indirect by inducing expression of other degradative proteinases, or by the direct action of collagenase on other substrates in the epidermis. Disruption of intercellular contact by degradation of collagenase-sensitive material between keratinocytes could be thought of as a type of microtrauma and might have triggered wound-healing processes leading to hyperproliferation of keratinocytes and regenerative maturation.

Manipulation of growth factors and related mechanisms

Various growth factors are upregulated in psoriatic lesions, including the EGF-like growth factors amphiregulin (Piepkorn, 1996), TGF-α (Elder *et al.*, 1989) and heparin binding epidermal-like growth factor (Stoll and Elder, 1998), VEGF (Detmar *et al.*, 1994), and nerve growth factor (Fantini *et al.*, 1995; Pincelli, 2000; Pincelli and Marconi, 2000). Each of these growth factors is also overexpressed during epidermal wound healing (James *et al.*, 1991; Frank *et al.*, 1995; Stoll *et al.*, 1997; Matsuda *et al.*, 1998; Shirakata *et al.*, 2005). Several of these factors have been overexpressed in transgenic mice with resulting psoriasis-like phenotypes, suggesting that these factors play a role in the formation and maintenance of psoriatic lesions. Amphiregulin and heparin-binding epidermal-like growth factor are heparin-binding members of the EGF family. Amphiregulin has distinct biochemical (Cook *et al.*, 1991) and biological (Chung *et al.*, 2005) properties from those of the non-heparin binding factors TGF-α and EGF. Transgenic expression of amphiregulin in the basal layer (*Tg(KRT14-AREG)3Pwc*, Table S1) resulted in a severe inflammatory skin phenotype characterized by prominent scaling, alopecia, papillomatous epidermal growths, inflammatory infiltrate of neutrophils and lymphocytes, and dilated blood vessels within the upper dermis (Cook *et al.*, 1997). Interestingly, some of these mice also developed arthritis (Cook *et al.*, 2004). Perhaps owing to the presence of massive inflammation, these animals had a markedly shortened lifespan and growth restriction. In contrast to this, when TGF-α was overexpressed in basal layer of the epidermis, *Tg(Tgfa)1Efu* (Vassar and Fuchs, 1991), only mild focal thickening of the skin and stunted hair growth

were observed. We were also unable to observe a hyperproliferative or inflammatory phenotype in transgenic mice engineered to overexpress heparin-binding epidermal-like growth factor in the basal layer (Stefan Stoll and James T Elder, unpublished data). Intraperitoneal injection of antibodies directed against amphiregulin inhibited the hyperplastic response in a xenograft model of psoriasis (Bhagavathula *et al.*, 2005), supporting the notion that this growth factor is important in the psoriatic pathomechanism. However, further studies are needed to determine whether amphiregulin is truly unique among EGF-like growth factors in its ability to elicit a psoriasiform phenotype.

In a mouse model in which VEGF was targeted to the basal layer of the epidermis (*Tg(KRT14-Vegfa)1Gdy*; Table S1), the mice developed a phenotype very similar to psoriasis (Xia *et al.*, 2003; Kunstfeld *et al.*, 2004). Histologically, the skin in these mice demonstrated hyperplastic and inflamed dermal blood vessels, epidermal thickening with aberrant keratinocyte differentiation, and characteristic inflammatory infiltrates. This phenotype could be reversed by a VEGF antagonist (Xia *et al.*, 2003). VEGF is a potent mediator of angiogenesis and its levels are elevated in psoriatic skin (Detmar *et al.*, 1994). Expression of the VEGF receptor was originally thought to be restricted to endothelial cells, but recent reports have demonstrated the presence of VEGF receptors on human keratinocytes (Wilgus *et al.*, 2005). Interestingly, VEGF signals through Stat3 (Bartoli *et al.*, 2003) and induces proliferation of normal human keratinocytes (Wilgus *et al.*, 2005). Thus, some of the phenotype seen in this model could be due to direct action of VEGF on keratinocytes. Whether antipsoriatic therapies showed any efficacy was not reported (Xia *et al.*, 2003; Kunstfeld *et al.*, 2004).

Another interesting mouse model, based on conditional expression of the tyrosine kinase receptor Tie2 (*Tg(Tek-tTA)1Dmt* × *Tg(TetOS-Tek)1Dmt*), was recently published (Voskas *et al.*, 2005, Table S1). This receptor binds angiopoietins and has been shown to control angiogenic remodeling (Sato *et al.*, 1995). Expression of Tie2 and the angiopoietins have been shown to be upregulated in human psoriasis (Kuroda *et al.*, 2001). With the activation of the transgene, the mice developed extensive erythema, with loosely adherent silver-white scaling. Histologically, the epidermis was thickened with elongation of the rete pegs, compact hyperkeratosis, and focal parakeratosis. Furthermore, an inflammatory infiltrate and neutrophilic microabscesses were seen with increased number of blood capillaries. Interestingly, complete resolution was seen when the mice were treated with CsA (Voskas *et al.*, 2005). Although CsA can have an effect on cells other than T cells, this generally requires much higher doses than required for treatment of psoriasis (Behnam *et al.*, 2005). Given the lack of information regarding the CsA dosing in this paper, it is unclear whether this improvement was because of the well-known immunosuppressive effects of CsA, or because of some other secondary effects of this drug, which are only seen at very high doses (Hernandez *et al.*, 2001).

To date, there are no published studies of mice overexpressing nerve growth factor in the epidermis. However, treatment of a mouse xenograft model of psoriasis with a pharmacologic inhibitor of nerve growth factor signaling led to clinical improvement (Raychaudhuri *et al.*, 2004).

T-cell-based mouse models of psoriasis

Several models have been established which aberrant T-cell function results in a phenotype similar to psoriasis. When severe combined immunodeficient mice (SCID mice) on an ICR background were reconstituted with minor histocompatibility-mismatched naive ($CD45RB^{hi}$) $CD4^+$ T cells, 100% of the animals developed skin lesions 4–8 weeks after the transfer (Schon *et al.*, 1997). The skin lesions had many features similar to psoriasis, including thickening and hyperkeratosis of the epidermal layer, parakeratosis, infiltration of immunocytes, and proliferation of blood vessels. A number of cytokines characteristic of psoriasis were upregulated, including IFN-γ, TNF-α, IL-1α, VEGF, and IL-6. Interestingly, reconstitution with $CD4^+$ memory/effector ($CD45RB^{lo}$) T cells did not lead to any phenotype, and coinjection of these cells with naive ($CD45RB^{hi}$) $CD4^+$ resulted in a less severe phenotype. Furthermore, these mice responded to CsA and ultraviolet light B treatment. No evidence of apoptosis, characteristic of graft-versus-host disease, was seen. It was shown that the skin infiltrating $CD4^+$ T cells were predominantly memory/effector cells ($CD45RB^{lo}$) (Hong *et al.*, 1999) and that coadministration of IL-12 greatly enhanced the disease phenotype, whereas antibodies against the common p40 subunit of IL-12 and IL-23 prevented disease development. Surprisingly, transfer of naive $CD45RB^{hi}CD4^+$ T cells from IFN-γ-deficient (C.129S7(B6)-*Ifng*^{tm1Ts}/J) mice led to delayed onset but otherwise identical disease. In contrast to psoriasis, no $CD8^+$ T cells were seen in the epidermis (Hong *et al.*, 1999). A similar inflammatory skin phenotype, which was also shown to be T-cell-dependent (Breban *et al.*, 1996), was seen in rats transgenically expressing high levels of HLA-B27 and human β_2-microglobulin (*Tg(HLA-B*2705, B2M)33-3Trg*; Table S1). However, these animals also developed multisystem inflammatory disease characterized by arthritis and colitis (Hammer *et al.*, 1990). Although overexpression of HLA-B27 in mice was not associated with skin disease, these mice can develop arthritis and nail changes if the mouse β_2-microglobulin gene is either knocked out (*B2 mtm1Unc*) or replaced with the human homologue (Khare *et al.*, 1995, 1996). Whether this difference is related to host genetic background or different levels of transgene expression remains to be clarified.

A T-cell-dependent inflammatory skin disease resembling psoriasis is seen in mice with a hypomorphic mutation of the gene encoding CD18 (*Itgb2*^{tm1Bay}) backcrossed to mice of PL/J background (PL.129S7-*Itgb2*^{tm1Bay}; Bullard *et al.*, 1996; Figure 2). β_2 integrins are leukocyte adhesion molecules exclusively expressed on hematopoietic cells and responsible for cell–cell contacts in a variety of inflammatory interactions (Kess *et al.*, 2003). The common β-chain (CD18) associates with four different α subunits, forming distinct functional

heterodimers termed lymphocyte function-associated antigen (LFA)-1 (CD11a/CD18), Mac-1 (CD11b/CD18), gp150,95 (CD11c/CD18), and CD11d/CD18 (Kess *et al.*, 2003). These interact with over 20 ligands, of which the most prominent belong to the ICAM (intercellular adhesion molecule) family (Carlos and Harlan, 1994; Springer, 1994). Interestingly, only the PL/J mice with the hypomorphic CD18 mutation (*Itgb2*^{tm1Bay}) backcrossed from 129S7 mice developed skin disease, but not mice expressing the wild-type or null (*Itgb2*^{tm2Bay}) alleles. Moreover, the disease did not develop in ICAM-1-deficient (*Icam1*^{tm1Bay}) mice (Sligh *et al.*, 1993). Likewise, no phenotype was observed when the mutation was backcrossed to different mouse strains (C57BL6/J or 129S7), indicating the existence of important modifier genes (Kess *et al.*, 2003). The inflammatory lesions were characterized by influx of immunocytes and expression of Th1 cytokines such as IFN-γ. However, in contrast to psoriasis (Uyemura *et al.*, 1993), the Th2 cytokine, IL-10, was also slightly increased. Interestingly, treatment with a monoclonal antibody against CD4$^+$ T cells resulted in complete remission, whereas antibodies against CD8$^+$ T cells had no effect (Kess *et al.*, 2003). Given the effect of the anti-CD4 antibodies, it is likely that this phenotype is due to either dysregulation or generation of autoreactive lymphocytes, as LFA-1 is one of the factors involved in the regulation of apoptosis during negative selection of autoreactive thymocytes (Quddus *et al.*, 1994). Furthermore, β_2 integrins are also crucial for the adjustment of antigen-dependent activation threshold of T cells (Bachmann *et al.*, 1997). This model was recently demonstrated to be dependent on TNF-α production by activated macrophages (Wang *et al.*, 2006).

Another model that should be mentioned in this context is the cutaneous inflammatory disorder observed in integrin α_E (CD103)-deficient mice (*Itgae*^{tm1Cmp}; Table S2; Schon *et al.*, 2000). The $\alpha_E\beta_7$ integrin is normally expressed by T cells in mucosal and epidermal sites and is thought to mediate intraepithelial retention of T cells (Sigmundsdottir *et al.*, 2004). Interestingly, the expression of this integrin is a marker for a subset of highly potent, functionally distinct regulatory T cells specialized for crosstalk within epithelial environments (Lehmann *et al.*, 2002). The phenotype of these mice would indicate that $\alpha_E\beta_7$ integrin is directly involved in the function or generation of these regulatory cells as loss of its expression results in such a severe inflammatory phenotype. The skin lesions in this model (Figure 2) were characterized not only by hyperproliferation of keratinocytes, hyperkeratosis, and increased vascularity, but also by ulcerative skin lesions, which are not a feature of psoriasis.

Mice lacking the transcription factor interferon regulatory factor (IRF)-2 (*Irf2*^{tm1Mak}; Table S2) developed an inflammatory skin disease, characterized by erythema, hair loss and increased proliferation of keratinocytes. Several abnormalities not characteristic of psoriasis were also observed, including a disorganized muscle layer and associated prominent fibrosis (Hida *et al.*, 2000). IRF-2 is thought to function as a negative regulator of gene expression by antagonizing IFN-α/β signaling. This is important as IFN-α has been implicated in the pathogenesis in psoriasis (Nestle *et al.*, 2005). Interestingly, this disease appeared to be predominantly mediated by CD8$^+$ T cells as selective depletion of these cell delayed the onset of the skin disease (Hida *et al.*, 2000).

More recently, a model based on the expression of an autoimmunity-prone $\alpha\beta$ TCR was developed (*Tg(TcraMM14.4,TcrbMM14.4)500Ach*; Table S1; Logunova *et al.*, 2005). Mice that have had their major histocompatibility complex class II peptide diversity reduced to a single complex may be prone to autoimmunity, and in this case developed significant numbers of ''autoreactive'' T cells, resulting in multisystem inflammation. Logunova and co-workers cloned one of the autoimmunity-prone TCRs (MM14.4) and transgenically expressed it with the result that mice developed an inflammatory skin disease resembling psoriasis (Figure 2). Interestingly, although this TCR was cloned from a CD4$^+$ T cell, the psoriasiform dermatitis was mediated by effector CD8$^+$ T cells (Logunova *et al.*, 2005).

The only other T-cell-dependent model, the constitutively active Stat3 model, was described earlier. As increasing number of data indicate that psoriasis is a T-cell-mediated disease (Gudjonsson *et al.*, 2004), with antigen-specific responses against an epidermal antigen (Johnston *et al.*, 2004), these T-cell-dependent animal models directly demonstrate and support the concept that T cells can induce psoriasiform skin lesions.

Models based on targeted cytokine expression

Several interesting transgenic models have been developed that overexpress some of the cytokines that characterize psoriasis. TNF-α is a cytokine that is overexpressed in psoriasis (Ettehadi *et al.*, 1994) and targeted therapy against this cytokine is a highly effective treatment in a significant majority of patients (Leonardi *et al.*, 2003), indicating that it has a central role in the disease process. Interestingly, overexpression of this cytokine in the epidermis of transgenic animals, *Tg(Krt14-TNF)1Efu*, led to retarded hair growth, inhibition of adipose production and signs of fibrosis, and immune infiltration in the dermis with subsequent necrosis and cachexia (Cheng *et al.*, 1992).

Another cytokine thought to be central in the pathogenesis of psoriasis is IFN-γ (Barker *et al.*, 1991). It is a prototypical Th1 cytokine and is a potent mediator of T-cell-mediated immune responses. Intradermal injection of IFN-γ into normal skin induced keratinocyte proliferation (Barker *et al.*, 1993), and psoriasis can be induced at the injection site of IFN-γ in uninvolved psoriatic skin (Fierlbeck *et al.*, 1990). Furthermore, T-cell clones isolated from psoriasis skin lesions have been shown to induce keratinocyte proliferation in an IFN-γ-dependent manner (Prinz *et al.*, 1994). Transgenic expression of IFN-γ in the suprabasal epidermal layer of mice (*Tg(IVL-Ifng)C1205Fmw*; Table S1) resulted in striking hypopigmentation of the hair due to the reduced abundance of melanocytes. Severely affected mice had reddened skin, growth retardation, hair loss, and flaky skin lesions. Keratinocyte proliferation was increased and there was epidermal thickening with spongiosis and parakeratosis and infiltration of inflammatory cells with a decrease in Langerhans cells,

a process having more resemblance to contact dermatitis or other eczematous processes than psoriasis (Carroll *et al.*, 1997).

Likewise, mice that were constitutively made to express the common p40 subunit of IL-12 and IL-23 in basal keratinocytes (*Tg(KRT14-Il12b)1Tsk*; Table S1) developed an eczematous skin disease that was characterized by hyperkeratosis, focal epidermal spongiosis, and inflammatory infiltrate (Kopp *et al.*, 2001). Subcutaneous injections of IL-12 resulted in a skin phenotype comparable to that of the p40 transgenic mice. IL-12 is a heterodimer of the p35 and p40 subunits and is a known inducer of IFN-γ (Trinchieri, 1995). IL-23 is a heterodimer of p40 and p19, but is functionally divergent from IL-12 and is thought to be a key player in chronic inflammation by inducing development of a separate T-cell subset characterized by IL-17 production (Langrish *et al.*, 2004). In a subsequent study (Kopp *et al.*, 2003), it was shown that this phenotype was due to epidermal production of IL-23, but not IL-12, and demonstrated that the phenotype could be reproduced by subcutaneous IL-23 injections. Interestingly, these mice also had enhanced cutaneous immunity as demonstrated by accelerated graft rejection (Kopp *et al.*, 2003).

Xenografts as models of psoriasis

Xenotransplantation offers an alternative approach to the transgenic expression of inflammatory mediators for the development of an animal model of psoriasis. These models, in which uninvolved non-lesional psoriatic skin or plaque psoriasis skin is transplanted onto severely immunodeficient mice, currently come closest to incorporating the complete genetic, phenotypic, and immunopathogenic processes of psoriasis (Wrone-Smith and Nickoloff, 1996; Boyman *et al.*, 2004). Several mouse strains have been used for this purpose (Table S3).

Nude mice

Initial investigations focused on athymic nude mice (Krueger *et al.*, 1981). Using this approach, it was shown that psoriatic features of transplanted affected skin could be maintained for more than 2 months without further manipulation (Fraki *et al.*, 1982). These mice possess a vestigial thymus, which is incapable of producing mature T cells. This results in impaired T-cell functions, as demonstrated by an absence of a delayed type hypersensitivity reaction, inability to reject skin allografts, and decreased antibody responses to some T-cell-dependent antigens. However, their response to T-independent antigens is normal and they have no defects in natural killer (NK) cell function (Meyerrose *et al.*, 2003).

SCID mice

SCID mice lack both humoral and cellular immunity due to a mutation in the DNA-dependent protein kinase (protein kinase, DNA-activated, catalytic polypeptide, *Prkdc*^{scid}) gene that is required for successful T-cell receptor and immunoglobulin gene rearrangements and thus is essential for T- and B-cell development. The SCID mutation also confers extreme radiosensitivity due to inability to repair double-stranded DNA breaks (Takahashi *et al.*, 2002). One well-utilized SCID mouse, CB.17-*Prkdc*^{scid}/*Prkdc*^{scid}, retains high NK cell numbers and function, whereas the SCID mutation on other backgrounds can be more amenable to engraftment, for example, non-obese diabetic/LtSz-*Prkdc*^{scid}/*Prkdc*^{scid} mice that have additional defects in NK and macrophage function. Although the SCID mice accept transplants of solid tissues, single-cell suspensions are rapidly recognized and lysed by mouse NK cells (Meyerrose *et al.*, 2003). Therefore, T-cell engraftment in this model is very poor. Although skin grafts are well accepted and maintained in these mice, the grafts gradually decrease in size (Takizawa *et al.*, 1995) and become hyperplastic (Nickoloff *et al.*, 1995), a feature that was less marked in more severely immunodeficient strains (Takizawa *et al.*, 1997). Despite this, SCID mice have been widely used for psoriasis research and are capable of maintaining the disease process for weeks to months in transplanted lesional skin. This model has also been used for evaluating efficacy of novel biologic agents in preclinical studies (Villadsen *et al.*, 2003). Nickoloff and co-workers showed that by injecting large numbers of autologous superantigen-stimulated blood-derived immunocytes under the transplanted non-lesional skin (PN) from a psoriatic patient, it was possible to induce conversion into psoriasis plaque skin (PP) in 9 out of 10 patients studied (Wrone-Smith and Nickoloff, 1996). Importantly, control skin from normal individuals showed no changes. This model demonstrated conclusively that psoriasis is a T-cell-mediated disease. However, its utility has been limited by its logistical complexities.

AGR129 mice

A novel xenotransplantation model was recently described (Boyman *et al.*, 2004), in which psoriatic skin lesions develop spontaneously when PN skin is engrafted onto AGR129 mice. AGR129 are triple knockout mice deficient in type I and type II IFN receptors and lacking the recombinase activating gene-*2* gene. These mice lack T- and B-cells and have immature NK cells with severely impaired cytotoxic activity *in vitro* and *in vivo* (Boyman *et al.*, 2004). Upon engraftment, resident human T cells in uninvolved psoriatic skin were shown to undergo local proliferation and activation. This is crucial for development of the psoriatic phenotype, as treatment of the grafts with anti-CD3 antibody prevented the conversion into lesional skin (Boyman *et al.*, 2004). The psoriatic phenotype developed in 28 out of 31 (90%) mice grafted. Phenotypic conversion started at week 4 and was fully developed by 6–8 weeks after engraftment. The development of the lesion was associated with expansion of T cells within the graft, especially the epidermal CD8 T cells (Boyman *et al.*, 2004). This model has already been used to elucidate novel pathogenic mechanisms in psoriasis (Nestle *et al.*, 2005).

Although the type I interferon defect in these mice may play a role in this spontaneous phenotype (Nestle *et al.*, 2005), several lines of evidence suggest that lack of host NK cell function is likely to be the critical factor. Mouse NK cells

may hinder the development and proliferation of the T cells residing in the graft (Meyerrose *et al.*, 2003), which is also highlighted by the fact that an absence of NK cell function can result in a 12- to 20-fold better engraftment by hematologic and immunologic cells, especially T cells (Shultz *et al.*, 2003). Moreover, in the presence of even suboptimal host NK activity, human T cells survive and undergo expansion after hematological xenotransplantation only if extremely high numbers of T cells are transplanted (Gorin *et al.*, 2002). In skin transplantation models, this can only be achieved by transplantation of lesional skin containing many activated T cells (Villadsen *et al.*, 2003) or by injecting large numbers of pre-activated T cells underneath the nonlesional graft (Wrone-Smith and Nickoloff, 1996). It is enticing to speculate that residual NK function in the early immunodeficient mouse models was the reason for graft shrinkage and why inflammatory processes diminish after several weeks of engraftment (Sugai *et al.*, 1998). Consistent with this hypothesis, it was recently demonstrated that killing of donor antigen-presenting cells in an allograft skin transplant model was mediated by host NK cells (Yu *et al.*, 2006). No studies have been carried out to address specifically this point in skin xenotransplantation.

In the AGR129 mouse model, non-psoriasis control (NN) skin did not transform to a psoriasis-like phenotype, which is consistent with the assertion that T cells residing in the PN skin are essential for the development of the lesion. This is supported by the effectiveness of anti-CD3 antibodies in preventing the PN to PP transformation in the AGR129 model (Boyman *et al.*, 2004). Given that PN skin has increased numbers of dermal and epidermal T cells compared with NN skin (Baker *et al.*, 1988), it is possible that NN skin contains too few T cells to propagate this transformation. However, it is likely that the difference between NN skin and PN skin is more than just sheer numbers of T cells. In the human SCID model, NN skin could not be converted to PN skin even when large numbers of activated autologous T cells are injected into the graft (Wrone-Smith and Nickoloff, 1996). Some tissue response was seen when NN skin was loaded with activated T cells, just as erythema and an increase in keratinocyte proliferation is seen following injection of IFN-γ into non-psoriatic skin (Fierlbeck *et al.*, 1990). The activated T cells are likely to release cytokines that promote local inflammation in NN skin, but we would speculate that in the absence of their cognate antigen, these cells do not trigger the development of a full-fledged psoriatic lesion. However, in psoriasis patients from whom increased circulating T-cell responses to potential epidermal autoepitopes have been demonstrated (Johnston *et al.*, 2004), the injected autologous T cells may recognize their cognate autoantigen in the graft and proliferate causing development of the psoriatic lesion.

Although the xenotransplant models are currently the best mouse models of psoriasis that we have, they have several limitations. They are technically difficult as they require large keratome sheets or multiple punch biopsies from patients, and the grafting needs to be performed quickly to minimize graft ischemia.

CONCLUSION

There is a frequent sentiment among scientists that an animal model must exactly mimic the human disease that is being studied. However, this goal is only rarely attained. Failure of an animal model to meet the criteria for a specific human disease is ascribed to four major sources (Sundberg, 1994): the animal system is incompletely or inaccurately described; the human disease is incorrectly or incompletely described; there are species-specific differences in biological processes that are important for the disease process; there are differences between inbred and outbred animals. In the Introduction, we discussed several differences in the cutaneous anatomy and the immune systems of mice and humans. Thus, even if the precise primary molecular defects in human psoriasis were known and could be transferred to mice, it is certainly possible that the resulting disease in mice would not look exactly like psoriasis in humans. Moreover, it is widely accepted that psoriasis is a polygenic disease, and most of the models developed by genetic engineering so far are based on single gene manipulations. Indeed, the fact that several mouse models do recapitulate most, if not all, aspects of the psoriatic phenotype (Figure 2) is very encouraging. The existence of these models indicates that there are well-conserved cellular interactions between the epidermis, dermis, vasculature, and inflammatory and immune cells that can be perturbed to produce a state of ''psoriasiform'' inflammation via derangement of specific molecules and pathways.

Although there is a great need for good animal models of psoriasis for manipulative or treatment studies, researchers should be careful not to choose a suboptimal or incorrect model. As can be seen in Figure 2, many of the mouse models only have incomplete information regarding their phenotypes, demonstrating that there is a definite need for a standardized scoring system that would enable researchers to compare different models and their compatibility to psoriasis. Such a scoring system has been suggested recently (Nickoloff, 2006).

One important caveat is that some of the mutations discussed may present as different phenotypes when expressed in mice of different background strains; for example, IL-1ra^{null} (*Il1rn*^{tm1Nick}; Shepherd *et al.*, 2004), CD18^{hypo} (*Itgb2*^{tm1Bay}; Kess *et al.*, 2003), and SCID (*Prkdc*^{scid}; Meyerrose *et al.*, 2003). Thus, careful selection, definition, and monitoring of strain background is of paramount importance.

Although the transgenic and knockout strains developed so far can and have been proven to be extremely useful for development and testing of therapeutics targeted against the specific pathway being disrupted, none of them have yet been used for large-scale testing or development of novel targeted treatments in psoriasis. To date, only the xenograft models have been used in that regard (Villadsen *et al.*, 2003). It should be emphasized that the xenograft models come closest to incorporating the complete genetic, phenotypic, and immunopathogenic processes of psoriasis, and currently have the greatest potential to increase our understanding of the pathomechanisms involved in psoriasis compared with other available mouse models. However, it is probable that with increased knowledge of the structure and function of the

genetic components involved in psoriasis susceptibility, we will be able to develop more tractable yet faithful animal models of this challenging disease.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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NOTE ADDED IN PROOF

Since submission of this manuscript a new model of psoriasiform hyperplasia has been described. In this model, psoriasiform hyperplasia (Djalilian *et al.*, 2006) was seen in mice lacking the transcription factor Krupple-like factor 4 (Klf4) and this was associated with upregulation of the gap junction protein connexin 26 (Cx26). Interestingly, ectopic expression of Cx26 reproduced the same phenotype.

SUPPLEMENTARY MATERIAL

Table S1. Details of the transgenes used in the models described in the text.

Table S2. Details of targeted mutations outlined in the text.

Table S3. Selected immunodeficient mouse strains suitable for xenotransplantation.

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